REMARKS

Status of the Claims

Claims 4-10 and 15-16 are currently pending. Claims 1-3, 11-14 and 17-24 were previously cancelled. Claim 4 is currently amended to make the language more clear and to claim specifically SEQ ID NOS: 15, 17 and 11. No new matter is added by these amendments.

Applicants respectfully request entry of the present amendments.

Interview

Applicants thank the Examiner for his time on October 4, 2010 for the phone interview to discuss the currently pending claims and proposed amendments to claim 4.

Claim Rejections – 35 U.S.C. §103

The Examiner has rejected claims 4, 5 and 8-10 under 35 U.S.C. §103(a) as being unpatentable over Schmidt et al. in view of Hemauer et al., and further in view of Lowe et al. (Action page 2) The Examiner asserts, in part, that one of ordinary skill in the art would have been motivated to modify the method of Schmidt to use primers of SEQ ID NOS: 15 and 17 and a probe sequence of SEQ ID NO: 11 because Schmidt demonstrates the benefits of designing and using similar primers and probes targeting the NS1 region, and because Hemauer provides Parvovirus B19 sequence and defines a conserved stretch of nucleotides comprising SEQ ID NOS: 15, 17 and 11, and Hemauer also designed nearby primers. Further, the Examiner asserts that the skilled artisan would have had a reasonable expectation of success in modifying the method of Schmidt to substitute for similar and equivalent primers and a probe derived from the same well-known and amplifiable conserved stretch of the NCS-1 region, resulting in the predictable amplification and detection of multiple different parvovirus sequence variants. (Action pages 4-5)

Applicants respectfully traverse the rejections. None of the cited references alone or in combination teach the specific sequences SEQ ID NOS: 15, 17 and 11, or the combination of these sequences, as provided in the instant claims. Applicants assert in the detailed discussion below that:

- there was no motivation for one skilled in the art to modify Schmidt in view of Hemaeur to achieve this specific combination of oligos as claimed, and in fact Hemauer teaches away from designing primers in this region,
- the Examiner has over-generalized the terms "homologs" and/or "equivalents" in the present context of nucleic acid amplification,
- the selection of the claimed sequences was not "obvious to try",
- there is no reasonable expectation of success based on the teachings of Lowe.

Schmidt and Hemauer

The Examiner asserts that Schmidt provides primers and a probe nearby the claimed sequences, and further asserts that Hemauer identifies a conserved stretch of sequence at position 2020-2240, this sequence comprising SEQ ID NOS: 15, 17 and 11. The Examiner concludes that Hemauer's teachings of amplification and detection of such a conserved region would motivate one of skill in the art to modify Schmidt to detect parvovirus using the presently claimed methods. (Action pages 3- 4)

As discussed in our Response filed March 4, 2010 ("prior Response", incorporated here by reference), Applicants assert that Hemauer provides that this amplification region is only "relatively conserved" in relation to the other regions discussed. It is notable that Hemauer's own oligos are designed OUTSIDE of this supposedly "conserved" region. Applicants assert that the Examiner is in error in drawing the conclusion from the limited data set in Hemauer that position 2020-2240 is the most conserved region of the parvovirus genome and therefore one skilled in the art would be inherently motivated to

design primers in this region. Hemauer provides that the NS region begins with nt 1950-2020, followed by a "relatively conserved stretch" 2020-2240; however Hemauer finds variability throughout this region and the entire parvovirus genome. (Hemauer p. 1783 right column 1st full paragraph) In fact, based on the relatively low number of base changes found by Hemauer in region 2985-3170 (Hemauer page 1784 top of right column), Hemauer teaches away from using the NS region because one of skilled in the art would have had a greater motivation to design primers in the 2985-3170 region because there were only 3 exchanges identified in the 2985-3170 region, compared to 12 exchanges in the 2020-2240 region. One skilled in the art would instantly realize that region 2985-3170 is more highly conserved in this data set than region 2020-2240.

If one skilled in the art were to be motivated to design oligonucleotides in region 2020-2240, as alleged by the Examiner, why didn't Hemauer design his primers in this region? Hemauer Fig 1 illustrates the multiple regions amplified, and those primers are summarized in Table 2. Hemauer does not provide teaching or suggestion to design oligonucleotides in the 2020-2240 region or any other area other than those provided in Table 2.

Further it is of interest to note that Schmidt page 229 under the "Nested PCR" section describes the primers as being directed to the VP1/VP2 region. While applicants acknowledge that the nt positions assigned to each oligo fall within the NS1 region as defined in Fig 1 of Hemauer, one of skill reading Schmidt could easily be confused about which area of the parvovirus genome was actually being detected. This confusion further supports Applicants' assertion that one of skill in the art would not look to Schmidt for guidance in designing a reliable and predictable parvovirus detection method.

Further, there are no problems or technical hurdles provided in Schmidt left to be solved ("...the assay is highly reproducible..." Schmidt p. 230 top right column) that would have motivated one skilled in the art to alter the oligos in Schmidt to arrive at the presently claimed invention.

Applicants assert that one skilled in the art would not look to Hemauer to modify Schmidt to arrive at the presently claimed invention.

Homologs and Obvious to Try

The Examiner asserts that the claimed primers and probe simply represent structural homologs, or "equivalents", which are derived from sequences suggested by the prior art, and that the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations. (Action pages 5-6) Applicants repeat the assertions from the prior Response that the Examiner is in error in citing MPEP 2144.06 because the term "structural homolog" in the context of nucleic acid sequences refers to a "degree of similarity between the sequences" and NOT the fact that they can hybridize to the same virus. Oligonucleotides that bind to the same gene tens or hundreds of bases apart are NOT homologs. As discussed in length in Applicant's prior Response, the parvovirus NS1 region is greater than 2 KB. Oligonucleotides that bind to different parts of this 2000 base pair region are definitely NOT "equivalents". The Examiner has over-generalized the terms of homologs and/or equivalents in the present context of nucleic acid amplification.

Applicants further assert in view of the cited prior art that the present invention was not "obvious to try". None of the cited prior art provides direction as to which of many possible choices of oligonucleotide design is likely to be successful when used in a method to detect parvovirus such as provided in the instant invention. The NS gene region is >2kb in length, which comprises hundreds of thousands of possible primer and probe sequences and combinations thereof. The Examiner has cited art providing various primer and probe designs throughout the entire parvovirus genome, which is almost 5kb in length. The "obvious to try" standard is erroneously equated with obviousness in this situation. The Federal Circuit (*Kubin* 561 F.3d 1359) has "outlined two classes of

situations where 'obvious to try' is erroneously equated with obviousness under § 103." The first situation is applicable here, wherein the invention is not obvious under 103 when:

> "...to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful results, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful", (*O'Farrell*, 853 F.2d 894).

It was not obvious to select SEQ ID NOS: 15, 17 and 11 or the combination thereof from the broad range and large number of possible oligonucleotides and combinations possible from the parvovirus genome. In the absence of specific direction from the prior art, it was not "obvious to try" to select the claimed sequences. The "obvious to try" standard is not applicable in this case.

Expectation of success

With regard to the issue of reasonable expectation of success in using such alleged equivalents, the Examiner asserts that Lowe provides evidence. (Action page 6) Applicants assert that the Examiner is in error in citing Lowe to prove equivalence of primers in the detection of a highly variable viral sequence target. In the specification as filed, Applicants provide a number of primer and probe sequences that are theoretically capable of amplifying parvovirus, but only one set of primers and probes were determined to work the best. Example 1 (specification, beginning at paragraph [0121]) provides criteria for selection of primer sequences:

- Tm 59-63°C
- no or less mismatches with published Erythrovirus sequences incl. recently discovered new variants (Nguyen Q. T. et al., Virology 301 (2002) 374-80; Servant A. et al., J. Virol. 76 (2002) 9124-34)
- less false priming sites

- primer should end with A or C

Lowe does not teach or suggest the use of such important criteria.

Example 1 in the specification concludes: "As evident here, STS17/18 {SEQ ID NOS: 15 and 17} has been chosen for further experiments since it comprises the lowest ct-values along with less deviation on ct-value basis." Further testing was done of the various primer combinations in subsequent examples, such as Example 3. As evident from these examples, even with the stringent selection criteria provided, not all primer designs will function in the method as expected. The determination of "successful" primer and probe combination does not simply mean it amplifies a predicted size and/or binds to an appropriate probe (as per Lowe's conclusions). In the scope of the invention, determination of the "best" oligonucleotides includes replicate testing and measurement by ct values in the context of amplification of a virus with highly variable sequences. These important assay characteristics, which are of high value to the detection of Parvovirus in a sample, are not predictable by a computer program such as described by Lowe.

Applicants assert that the selection of oligonucleotides is unpredictable, as evidenced by Example 1 as discussed above. Lowe does not provide sufficient teachings to design primers and probes that consistently perform in a complex detection assay in a predictable fashion.

Summary

The Examiner has not provided a basis for combining the cited references, and no motivation or reasonable expectation of success is provided in the rejections aside from a conclusory statement that the known existence of the Parvovirus sequence was a sufficient motivation to design the claimed primers. The Examiner is reminded that a specific motivation and reasonable expectation of success must be set forth in the rejection: "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these

"identified, predictable" solutions may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." (*Eisai Co. Ltd. V. Dr. Reddy's Laboratories Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008))

Applicants respectfully assert that one of ordinary skill in the art would NOT have been motivated by the teachings of the cited prior art to arrive at the instant invention for the reasons stated above. The combination of the cited prior art does not teach all of the elements of the instant claims, specifically SEQ ID NOs. 11, 15 and 17 and the combination thereof. None of the other art cited by the Examiner in addition to Schmidt, Hemauer and Lowe make up for the deficiencies in disclosing the claimed elements. Further, Applicants assert that a general motivation to search for additional oligonucleotide sequences that exist within a 2,000 bp region does not make the specific oligonucleotides identified in this unpredictable process *prima facie* obvious.

Therefore, the Examiner has not presented a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the §103(a) rejections of claim 4 and its dependents.

CONCLUSION

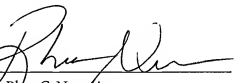
Applicants respectfully request entry of the present amendments and remarks. In view of the above, Applicants believe all claims now pending in this Application are in condition for allowance. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-730-8566.

Applicants respectfully request a 1-month extension of time to respond to the Office Action notification date June 7, 2010. The response date was September 7, 2010; with the granting of this request, the response time is re-set to October 7, 2010. The commissioner is hereby authorized to charge the amount of $ 130, the fee due under 37 CFR §1.17(a)(1) to Deposit Account No. 50-0812. Please grant any additional extensions of time that may be required to enter this amendment and charge any additional fees or credit any overpayments to Deposit Account No. 50-0812.

Please direct all future correspondences to: Customer No. 22829.

Respectfully submitted,

Date: October 7, 2010

By: 

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